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EXAMINER	
BORIN, MICHAEL L	

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1631	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/171,928	Applicant(s) Inomata et al.
	Examiner Michael Borin	Art Unit 1631

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jul 23, 2002* .

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *6, 8-11, and 21-29* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *6, 8-11, and 21-29* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of Claims

1. Amendment filed 07/25/02 is acknowledged. Claims 12-14 are canceled. Claims 28,29 are added. Claims 6, 8-11, 21-29 are currently pending.

In regard to claims 21,23,25,27, the claims were withdrawn from consideration as being drawn to a distinct invention. Applicant argues that claim 21 has been already addressed in previous Office actions and that claim 21 corresponds to original claim 7 (drawn to treatment of chronic heart failure, the latter being a result of cardiac hypertrophy). Although Examiner maintains that heart failure can be caused by etiologies unrelated from cardiac hypertrophy (such as myocardial infarction, cardiomyopathy or chronic hypertension), Examiner rejoins claims 21,23,25,27 with the understanding that they address heart failure being a result of cardiac hypertrophy. Claims 21,23,25,27 are included in the rejections of record.

2. Applicant's arguments have been fully considered and they are deemed to be persuasive-in-part. Rejections not reiterated from previous Office actions are hereby withdrawn. The following rejections constitute the complete set presently being applied to the instant application.

Discussion of calculations of dosage ranges.

3. Applicants arguments in regard to dose calculations were considered and deemed to be persuasive-in-part. Examiner agrees that the plasma level of 0.5 ng/ml in rats is supported by the disclosure. However, Examiner continues to disagree with the approach taken to recalculate concentrations in rats into concentrations in humans. Applicant provides in support several more publications. Combining data from these publications (page 9, last paragraph, of the response), applicant liberally averages the results obtained under different conditions and arrives at the average plasma level which seems to be close to the one expected. However, the results compiled by the applicant demonstrate that the same dosage of ANF, 0.025 μg/kg/min, may produce plasma level different by about two-fold, from 446 to 811 pg/ml.Examiner maintains that given multiple variables involved in the recalculations, a single dosage disclosed in the specification for rats can not be recalculated into a precise single value of a corresponding dosage for humans.

Claim Rejections - 35 USC § 112, first paragraph.

4. As follows from the discussion in the preceding paragraph, claims 26,27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled

in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Claim 26 introduces new matter by using the term "the effective amount is 0.025 μg/kg/min. There is no disclosure in the specification of such dosage used in the treatment of cardiac hypertrophy. As for recalculation of dosages for ANF from rat to human, see discussion above.

5. Claims 6,8-11,21-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for preventing or treating cardiac hypertrophy is rats using ANF at dosages which do not cause hypertensive or diuretic effect, does not reasonably provide enablement for (1) treatment of cardiac hypertrophy with ANF in species other than rats at dosages which do not cause diuretic and hypotensive effects; (2) treatment of cardiac hypertrophy with agents other than ANF and at dosages which do not cause diuretic and hypotensive effects; (3) treatment, in any species and with any agent as claimed, at plasma levels, such as in claims 22,24,26, or, more specifically, at dosage as claimed in claim 26.

The specification is limited to demonstration of one agent (ANF) and in one type of species (rats). In regard to (1) use in humans, applicants speculate that the data on rats can be extrapolated to other species. There is no support that rat model is an

adequate animal model for cardiac hypertrophy, and that mechanisms effect of effect of ANF, and sensitivity of receptors to ANF is the same in rats in humans.

In regard to (2), as applicants argue that the finding of the effect of ANF without involving hypotensive and diuretic effect is unexpected and unusual, the art in this regard is deemed unpredictable, and it is not clear whether other agents will have same specific mechanism of action.

In regard to (3), Examiner remains unconvinced that effects on rats can be recalculated and transferred to the effects on humans. Further, see discussion above about recalculations of dosage ranges made by applicant.

Response to arguments

Examiner agrees that specification is enabled for the treatment of cardiac hypertrophy; accordingly the first objection in this rejection in the previous Office action is withdrawn.

In regard to use in humans, applicants speculate that the data on rats can be extrapolated to other species. Please provide support for this statement using references which demonstrate that rat model is an adequate animal model for cardiac hypertrophy, and that mechanisms effect of effect of ANF, and sensitivity of receptors to ANF is the same in rats in humans.

In regard to (2), as applicants argue that the finding of the effect of ANF without involving hypotensive and diuretic effect is unexpected and unusual, the art in this regard is deemed unpredictable, and it is not clear whether other agents will have same specific mechanism of action.

In regard to (3), Examiner remains unconvinced that effects on rats can be recalculated and transferred to the effects on humans.

Claim Rejections - 35 U.S.C. § 102 and 103.

6. Claims 6,8,9,21,23,25 are rejected under 35 U.S.C. 102(b) as anticipated by Blaine et al. (US Patent 4652549) as evidenced by Espiner[1].

Blaine teaches method of treatment of cardiac hypertrophy using continuous administration of atrial natriuretic peptide (ANF) and fragments thereof. See abstract, summary, claims 1-8. The method step in Blaine, administration of ANF in anti-cardiac hypertrophy amounts, is the same as in the instantly claimed method. Further, the amount of ANF (or its analogs) in Blaine appears to be substantially lower that in the instant method: The dosage of ANF administered to hamsters, mice and rats in the

[1]Note that, although the date of the "Espiner" reference is later than the priority date of the instant application, the reference is a review describing studies preceding the instant application; the reference is used merely to demonstrate well known mechanisms of action.

referenced method is in amount of from about 10 to about 2000 picomoles/kg/min. If recalculated into the units used to describe the instant method, μg/kg/min, the referenced concentrations are equivalent to 0.00003 to 0.07 μg/kg/min [2]. The lower limit of this range is several orders less then 0.1 μg/kg/min used for same animals in the instant method, and the upper limit is about the same as in the instant method. Note that applicant asserts, contrary, that amounts of ANF used in the instant method are lower than those used in the prior art.

Further, it is well known that ANF, as well as its analogs, stimulate guanylate cyclase A and production of cGMP. See, e.g., Espiner, p. 205, last paragraph. Therefore, these claimed effects of ANF are inherently present. As for the claim limitation "amount... not effective for diuretic and hypertensive effects", the reference is silent about the presence of such effects of ANF. Demonstration of reduction in water content described in the reference does not amount to demonstration of a diuretic effect (as was asserted by applicant). Note that prior art acknowledges that, first, natriuretic peptides have a wide range of actions, and, second, hypertrophy is a result of an interaction between a variety of different interrelated signaling pathways. See, for example, Espiner, p. 205, right column, lines 30-33; Hefti,

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[2] For recalculation, Examiner used the notion in the specification (p. 17, last line) that 426±53 pg/ml ANF is approximately 0.14 nM)

p.2873, summary. Therefore, it is not possible to discern which particular mechanism was engaged in achieving an overall effect of treatment. Even though separate mechanisms might have been demonstrated in specifically designed model conditions, Examiner assumes that the referenced method inherently included the effect as instantly claimed. Since the Office does not have the facilities for examining and comparing applicants' method with the method of the prior art, the burden is on applicant to show that the referenced method did not include the effect as instantly claimed. So far applicant provided arguments about potential differences in the mechanisms of action of ANF in the claimed and referenced methods, but did not provide a clear demonstration that 10-2000 picomoles/kg/min of ANF used in the reference do not have the effect as instantly claimed, or that the effect of the referenced concentration is exclusively limited to diuretic/natriuretic action.

Therefore, the referenced method anticipates the instantly claimed method of treatment of heart disease based on hypertrophy comprising administration of a substance that acts on natriuretic receptor, guanylyl cyclase A and is able to accelerate production of cGMP.

In regard to claims 21,23,25, chronic heart failure is a disease based on cardiac hypertrophy.

In regard to claims 22, 23, reciting that ANF is administered in the amount sufficient to achieve plasma concentration of about 0.5 ng/ml, the referenced method uses ANF in the dosage range upper limit of which is about the same as in the instant method (0.07 *vs* 0.1 μg/kg/min); the ANF is administered to the same animals (rats). Thus, it seems that the referenced method is also capable to yield plasma concentration of about the same level as instantly claimed.

In regard to claims 24,25, example 11 in the reference demonstrates administration for 7 days.

Response to arguments

Applicants argue that the result in Blaine is totally different from the instant method. Examiner disagrees. In both cases the total weight of the heart decreased, and Blaine, as well as the applicants, claims reduction of cardiac hypertrophy. The method step in Blaine, administration of ANF in anti-cardiac hypertrophy amounts, is the same as in the instantly claimed method. Further, the amount of ANF (or its analogs) in Blaine appears to be substantially lower that in the instant method: The dosage of ANF administered to hamsters, mice and rats in the referenced method is in amount of from about 10 to about 2000 picomoles/kg/min. If recalculated into the units used to describe the instant method, μg/kg/min, the referenced concentrations are equivalent to 0.00003 to 0.06 μg/kg/min, which is several orders less then 0.1 μg/kg/min used

for same animals in the instant method (see Examples). Note that, contrary, the applicant asserts that the instant method utilizes amounts of ANF lower than those used in the prior art. Further, demonstration of reduction in water content described in the reference does not amount to demonstration of a diuretic effect (as was asserted by applicant).

It is also noted that applicants refer to results of clinical trials on humans; these results, however, are not a part of the instant disclosure.

7. Claims 6,8,9,21,23,25 are rejected under 35 U.S.C. 103(a) as obvious over Blaine in view of Cao et al. (Hypertension, 25, 227-234, 1995).

The primary reference (as discussed above) teach treatment of cardiac hypertrophy by natriuretic peptides. The primary references do not teach that the reduction of heart weight achieved as a result of the treatment excludes, specifically, such mechanisms as diuretic or hypotensive effects.

Cao et al teaches that (1) Cardiac hypertrophy include stimulation of gene cascade; (2) natriuretic peptides reduce stimulation of this cascade, as evidenced by a decrease in thymidine incorporation. Thus, the reference suggests that "such growth-suppressing activity raise the intriguing possibility that [natriuretic peptides] may function in paracrine fashion to modulate growth in the interstitial compartment

during cardiac hypertrophy. See p. 227, bottom. (3) Demonstrates that the hypertrophy-reducing effect of the natriuretic peptides is due to their interaction with guanylyl cyclase A natriuretic peptide receptor and is further mediated by formation of cGMP (p. 231, and p. 233, second paragraph).

Therefore, it would be obvious to one skilled in the art that cardiac hypertrophy can be reduced by natriuretic peptides by mechanisms other than hypotensive or diuretic, such as via interference with gene activation, and that the effect of treating cardiac hypertrophy described in the referenced methods might have included mechanism other than hypotensive or diuretic.

Response to arguments

Applicants argue that Cao reference mentions 1 μM concentration of ANF and lower doses could not have been predicted. However, the primary reference, Blaine, utilizes much lower doses as discussed above.

8. Claim 10 is rejected under 35 U.S.C. 103(a) as obvious over Blaine et al. in view of Espiner.

The Blaine reference is applied for the reasons set forth in the rejection of claims 6,8-10,21,23,25 over Blaine. In regard to claim 10, Espiner teaches that BNP

is a functional equivalent of ANF. See p. 205, right column through p. 206, left column.

9. Claims 11,28,29 are rejected under 35 U.S.C. 103(a) as obvious over Blaine.

The reference is applied as above. If there are any differences between Applicant's claimed methods and that of the prior art, the differences would be appear minor in nature. Although the prior art do not teach all particular ways of administration, selection of ways and forms of administration would be conventional and within the skill of the art. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal conditions of administration which are art-recognized result-effective variable which would have been routinely determined and optimized in the pharmaceutical art.

Conclusion.

10. No claims are allowed

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP §

706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (703) 305-4506. Dr. Borin can normally be reached between the hours of 8:30 A.M. to 5:00 P.M. EST Monday to Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. Michael Woodward, can be reached on (703) 308-4028. The fax telephone number for this group is (703) 305-3014.

Any inquiry of a general nature or relating the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MICHAEL BORIN, PH.D
PRIMARY EXAMINER